

# PATENT SPECIFICATION

NO DRAWINGS

**974.054**

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Date of Application and filing Complete Specification Oct. 15, 1962.  
No. 38875/62.

Application made in Sweden (No. 10596) on Oct. 25, 1961.

Complete Specification Published Nov. 4, 1964.

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Index at acceptance:—C3 P(4D1A, 4T2D); C3 A2; C3 U(2C, 2D, 2E, 3)

International Classification:—C 08 f (C 08 b)

## COMPLETE SPECIFICATION

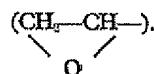
### A Method for the Manufacture of High Molecular Weight Hydrophilic Copolymers of Hydroxyl Group-containing Uncharged Polymer Substances in Gel Grain Form

We, AKTOEBOLAGET PHARMACIA, a Swedish Company, of 2, Sofieldundsgatan, Uppsala, Sweden, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention pertains to an improved method for the manufacture of high molecular weight hydrophilic copolymerisates of hydroxyl group-containing non-ionic polymer substances in gel grain form. More particularly the invention pertains to an improved method for the manufacture of high molecular weight hydrophilic copolymerisates in gel grain form by the reaction of hydroxyl group-containing non-ionic polymer substances with a bifunctional organic substance capable of reacting with the hydroxyl groups of the uncharged polymer substances with formation of ether bridges, as a cross-linking agent in the presence of an alkaline reacting substance.

As examples of suitable hydroxyl group-containing uncharged polymer substances for this reaction may be mentioned polysaccharides (such as dextran, starch, dextrin, cellulose, polyglucose) and hydroxyl group-containing uncharged derivatives of these substances (such as methyl dextran, ethyl dextran, hydroxy-propyl dextran, methyl cellulose, ethyl cellulose, ethylhydroxyethyl cellulose) or products obtained by a partial depolymerization of the same, as well as fractions thereof, and polyvinylalcohol.

The bifunctional organic substance is preferably of the type  $X-R-Z$ , in which R stands for an aliphatic residue, containing 3—10 carbon atoms, and X and Z are each halogen or epoxy, the latter being each linked with a carbon atom of the aliphatic residue to form an oxirane group



Examples of suitable bifunctional compounds for the above reaction are epichlorohydrin, dichlorohydrin, 1,2-3,4-diepoxybutane, bis-epoxypropyl ether, ethylene glycol-bis-epoxy propyl ether and 1,4-butane-diol-bis-epoxypropyl ether.

The aliphatic chains forming the cross-linking bridges of the copolymerisate are accordingly substituted, preferably with hydroxyl groups, and/or interrupted by heteroatoms, preferably oxygen atoms.

The molecular proportions of the organic hydroxyl group-containing substance to the bifunctional substance should be 1:at least 10.

The above-mentioned copolymers are especially to serve as molecule-sieving mediums, for which purpose they are to be used in the form of gel grains. For this purpose, and this also applies with respect to other presumable purposes of the copolymers in grain form, it is of great importance that the products should be obtained in this form directly as a result of their manufacture without any grinding of the copolymer and subsequent sieving of the ground product thus obtained being necessary.

The object of this invention is, therefore, to provide a process for the direct manufacture of the above identified copolymers, not requiring any disintegration of the reaction product obtained.

In the specification and claims the term "copolymer" is used to define a product obtained by the chemical combination of a number of similar units to form a single molecule wherein polymerisation phenomena as well as condensation reactions have been involved.

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The novel improved process according to the invention for the manufacture of the above-identified copolymers which comprises reacting, in the presence of alkaline reacting substance, a hydroxyl group-containing non-ionic polymer substance with a bifunctional organic substance, is characterized by mixing a liquid solution of the non-ionic polymer substance with a dispersing medium capable 5 of forming a two-phase system therewith, under sufficient agitation conditions to convert this liquid solution into drops suspended within the medium and by reacting the cross-linking agent with the non-ionic polymer 10 substance in the presence of the alkaline reacting substance, at least until gel formation has taken place, whereupon the gel grains of the copolymers formed from the drops, are recovered.

15 20 The alkaline reacting substance required for the reaction is usually contained in the solution of the non-ionic polymer substance, but it is also possible to supply the alkaline reacting substance dissolved in the liquid 25 forming the continuous phase of the two-phase system. There is, however, nothing to prevent forming the two-phase system first, after which the alkaline reacting substance is supplied in dissolved form into the two-phase 30 system mixture to induce the cross-linking reaction.

In principle, any substance presenting alkaline properties in solution can be used for the reaction. The alkali-metal hydroxides 35 such as sodium hydroxide are, however, the most frequently used alkaline substances. Such substances as quaternary ammonium compounds, the alkali metal and alkaline earth metal carbonates and the alkaline earth 40 metal hydroxides may also be used.

In order to effect the reaction according to the invention, it is advisable to proceed in such a way that a solution of the alkaline reacting compound and the hydroxyl group-containing non-ionic polymer substance is 45 mixed with that liquid which is to serve as the continuous phase of the two-phase system, under sufficient agitation conditions to attain the desired sizes of the suspended drops, 50 whereupon the cross-linking agent is supplied into the two-phase system, if desired, in a stepwise manner. The cross-linking agent may, however, also be supplied into the two-phase system dissolved in the liquid serving 55 as the continuous phase.

The above-mentioned sequence of the different operations of the process according to the invention has proved advisable in practice, but it is also possible to contact 60 a portion of the cross-linking agent or the whole amount thereof with the solution of the uncharged polymer substance before the two-phase system has been formed. In this connection, gel formation has to be prevented 65 from taking place before the two-phase sys-

tem has been formed. This can be attained by maintaining the mixture at a sufficiently low temperature to cause the reaction to proceed so slowly that the mixing operation can be carried out. The gel formation can also be prevented from taking place by keeping back the alkaline reacting substance, the latter being supplied only after the drop formation has taken place.

70 For most of the substances which may be used for the process according to the invention, such as starch, dextran, cellulose and similar substances, water will be the suitable solvent, but other liquids having similar solubility properties, such as alcohols and ketones, may also be used. If desired, solvent mixtures may be used in which water is the main component. It is preferable to use an alkali metal hydroxide as the alkaline reacting substance serving as a catalyst for the cross-linking reaction and as an accepting agent when the hydrogen halide is liberated, said alkali metal hydroxide being added to the water or aqueous liquid used for dissolving the polymer to be copolymerized. In many cases the alkali metal hydroxide will facilitate the dissolution of the uncharged polymer and increase its solubility. This especially applies with respect to the use of the polymer substances, dextran and starch.

75 80 85 90 95 The concentration of the hydroxyl group-containing substance is of great importance because it determines the swellability (water regain) of the final copolymerisate. Using a low concentration of the hydroxyl group-containing uncharged polymer substance will result in a higher swellability of the final product than when a higher concentration thereof is used. For dextran the concentration of the polymer can be 5 to 70 per cent, by weight, good results having also been obtained while using concentrations in the range of from 10 to 50, inclusive, per cent, by weight. With respect to cellulose derivatives, even lower concentrations of the uncharged polymer compound can be used.

100 105 110 115 120 To form the continuous phase of the two-phase system may be used liquids immiscible with water or with the substance used as a solvent for the hydroxyl group-containing polymer substance. Suitable solvents are aliphatic and aromatic hydrocarbons, halogenated aliphatic and aromatic hydrocarbons, such as dichloromethane, 1,2-dichloroethane, 1,2-dibromoethane and o-dichlorobenzene, when the hydroxyl group-containing polymer substance is dissolved in water.

125 In order to stabilize the dispersion of the solution of the hydroxyl group-containing non-ionic polymer compound it is advisable, according to the invention, to add a stabilizing agent to the liquid forming the continuous phase. As a stabilizing agent may be mentioned high molecular weight polymers

insoluble in water, such as polyvinylacetate, polystyrene, polyisobutylene and cellulose-acetate-butyrate. It has proved that the molecular weight of the high molecular weight polymers determines, to a considerable degree, their action as stabilizing agents, high molecular weight polymers having relatively high average molecular weights being capable of stabilizing the dispersion more effectively than products having lower average molecular weights under equal conditions for the rest. It is advisable to refer the amount of stabilizing agent to the content of that solvent which forms the continuous phase, having the cross-linking agent dissolved or in which it is dissolved on the formation of the two-phase system. Suitable amounts of the stabilizing agents are in the range of from 0.1 to 15, inclusive, grams, preferably in the range of from 0.1 to 10, inclusive, grams per 100 ml. of continuous phase. The stabilizing agent can be removed from the gel grains formed by treating the latter with a suitable solvent. With respect to high molecular weight polymers capable of undergoing hydrolysis under relatively mild conditions, it will be advisable first to treat the gel grains with a hydrolysing agent, for example a solution of alkali metal hydroxide, and then remove the hydrolysed products by washing the gel grains with a solvent for these products. High molecular weight esters such as polyvinylacetate and cellulose-acetate-butyrate, can be treated with a dilute aqueous solution of an alkali metal hydroxide to effect saponification of the esters, after which the high molecular weight alcohols formed are removed by washing with a suitable solvent. Under certain conditions it will be advisable to add a surface-active agent of the detergent type to the reaction mixture. Such agents do not act as suspension stabilizing agents, but can be used in combination with such agents when it is desirable to attain special effects such as smaller sizes of the copolymerise obtained. During the first period of the copolymerization process, the conditions of agitation are particularly important, these conditions and the presence of stabilizing agent determining the liquid drop sizes of the dispersed phase. In this connection, the skilled person will be capable, by examining samples taken out from the reacting mixture, at different agitation speeds, to determine the agitation speed necessary to attain a desired result. It is frequently advisable to add the bifunctional substance to the system only when suitable drop sizes have been attained. The time at which gel formation takes place depends on the content of hydroxyl group-containing uncharged polymer in the dispersed phase, the amount of bifunctional substance, the temperature, and the like. The reaction will, however, proceed until the bifunctional substance has been consumed or the reaction is interrupted. After the gel formation has taken place the agitation will be of no, or less, importance for the particle sizes of the final copolymerise. The reaction temperature will determine the speed at which the copolymerization takes place. Suitable temperatures are between room temperature and 90°C., preferably in the range of from 20 to 60°C. The property which determines the quality of the copolymer as a molecule sieve is its water regain. The latter is determined by swelling the product in water and removing the remaining free liquid, for example, by centrifuging. The water regain is stated in number of grams of the combined water per gram of the dry substance. The present copolymers have been tested for molecule sieving purposes in connection with which excellent results have been obtained due to the fact that the grains are ball-shaped and accordingly present a lower flow resistance when packed together than columns comprising gel grains of copolymers obtained by grinding or other disintegration operations. Particularly in respect of separating mixtures of sensitive compounds, such as those contained in biological liquids, for which purpose the time period during which the liquid can be permitted to be exposed to the separating medium is strongly limited, the present process products have proved extraordinarily valuable. The following examples are illustrative of preferred embodiments of the present invention. It should be understood that these examples are not intended to limit the invention and that obvious changes may be made by those skilled in the art without changing the essential characteristics and the basic concept of the invention. The percentages are by weight. The temperature is room temperature, and the pressure is atmospheric. The weight of gel grains referred to in the examples means the dry weight of the gel grains before swelling.

EXAMPLE 1

Dextran having an average molecular weight ( $M_w$ ) amounting to 40,000 is moistened with about 20 per cent of water, and to the mixture is added an aqueous 6 N solution of sodium hydroxide. After 1 hour a solution will be formed without formation of lumps. The amount of 6 N sodium hydroxide is so adjusted that the concentration of the solution will be 40 per cent. 600 g. of the dextran solution obtained are poured into a cylindrical reaction vessel provided with a stirrer and a thermometer. As a suspension stabilizing agent are added 20 g. of polyvinylacetate having an average molecular weight of 430,000 dissolved in 500

ml. of toluene, which latter serves as a suspending medium. The stirrer is put into operation and adjusted to such a speed that the aqueous phase will be dispersed in the form of small drops within the toluene phase. There are then added 50 g. of epichlorohydrin as a bifunctional substance or cross-linking agent. The reaction mixture obtained is maintained under agitation at 50°C. until the substantial amount of the epichlorohydrin has reacted.

The reaction process is controlled by taking out samples from the reacting mixture once an hour, the content of epichlorohydrin being estimated in the samples after separating off the grains suspended therein. Gel

Distribution of size: 50% 30-50 mesh  
35 water regain: 36% 40-100 mesh  
3.0 g./g. of the dry substance.

EXAMPLE 2

In a manner similar to that set forth in Example 1, there is formed an aqueous 40 per cent solution of dextran having an average molecular weight amounting to 40,000.

480 g. of this solution is poured into the cylindrical reaction vessel and to the solution are added 84 ml. of epichlorohydrin as a cross-linking agent and 30 g. of the polyvinylacetate set forth in Example 1 as a

Size distribution: 22% 30-50 mesh  
53% 50-100 mesh  
Water regain: 2.2 g./g. of dry substance.

EXAMPLE 3

60 In a manner similar to that set forth in Example 1 there is formed an aqueous 40 per cent solution of dextran having an average molecular weight amounting to 40,000. 480 g. of this solution is poured into the cylindrical reaction vessel set forth in Example 1,

65 and to the solution are added 70 ml. of epichlorohydrin as a cross-linking agent and 20 g. of polyvinyl acetate of the same kind as set forth in Example 1 as a suspension stabilizing medium dissolved in 500 ml. of dichloromethane. The cross-linking reaction is caused to proceed at 50°C. resulting in a nearly quantitative yield of copolymer of dextran with epichlorohydrin presenting a water regain amounting to 2.8 g./g. of the dry substance.

75 Size distribution of gel grains: 85% passing the 50 mesh sieve.

EXAMPLE 4

80 In a manner similar to that set forth in Example 1, there is formed an aqueous 40 per cent solution of dextran having an average molecular weight amounting to 40,000. 480 g. of this solution are placed in a cylindrical reaction vessel, and to the solution

85 Size distribution of gel grains:

115 56% 30-50 mesh  
20% 50-100 mesh

formation takes place after a reaction period of 1 hour.

After the completion of the reaction the suspension is worked up. The suspending medium is separated off from the gel grains by filtration, and the suspension stabilizer is washed off with toluene. After washing with alcohol to remove the solvent and then with water to neutral reaction, the copolymer obtained is dried at 110°C. The yield of copolymer, calculated on dextran, will be substantially quantitative.

The gel grains of the copolymer of dextran with epichlorohydrin are sieved to estimate their sizes, and the water regain is also determined.

Distribution of size: 50% 30-50 mesh  
36% 40-100 mesh  
3.0 g./g. of the dry substance.

EXAMPLE 5

suspension stabilizing agent dissolved in 500 ml. of o-dichlorobenzene as a suspending medium, whereupon the reaction is caused to proceed at 50°C. resulting in a nearly quantitative yield of copolymer of dextran with epichlorohydrin.

The gel grains of the copolymer of dextran with epichlorohydrin are sieved to estimate their sizes, and the water regain is determined.

50 Size distribution: 22% 30-50 mesh  
53% 50-100 mesh  
Water regain: 2.2 g./g. of dry substance.

are added 70 ml. of epichlorohydrin as a cross-linking agent and 20 g. of polyvinyl acetate of the same kind as set forth in Example 1 as a suspension stabilizing medium, both dissolved in 500 ml. of 1,2-dibromoethane. The cross-linking reaction is caused to proceed at 50°C. resulting in a nearly quantitative yield of copolymer of dextran with epichlorohydrin having a water regain amounting to 3.2 g./g. of the dry substance.

90 EXAMPLE 5

In a manner similar to that set forth in Example 1, there is formed an aqueous 40 per cent solution of dextran having an average molecular weight amounting to 40,000. 240 g. of this solution are poured into a cylindrical reaction vessel and to the solution are added 35 ml. of epichlorohydrin as a cross-linking agent and 2.5 g. of polyvinyl acetate of the same kind as set forth in Example 1 as a suspension stabilizing agent, both dissolved in 500 ml. of 1,2-dichloroethane. The cross-linking reaction is caused to proceed at 50°C. resulting in a nearly quantitative yield of copolymer of dextran with epichlorohydrin having a water regain amounting to 2.5 g./g. of the dry product.

100 56% 30-50 mesh  
20% 50-100 mesh

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## EXAMPLE 6

There is formed a solution of dextran having an average molecular weight ( $M_w$ ) amounting to 40,000 by dissolving 120 g. of the dextran product in 800 ml. of water and adding 60 ml. of an aqueous 5N solution of sodium hydroxide thereto.

A solution of 15 g. of cellulose acetate-butyrate (Cellit—Registered Trade Mark—BP 900 manufactured by the German Company Bayer in Leverkusen) in 500 ml. of ethylenedichloride is then prepared. The solution obtained is poured into a 2 litre wide-necked spherical reaction vessel provided with a stirrer and a thermometer. The temperature of the solution is adjusted to about 50°C. and the agitation speed to 200 revolutions per minute. The solution of dextran is then added successively to the solution of the high molecular weight substance in ethylenedichloride. One hour after the addition of the whole amount of the solution of dextran, uniform drops will be formed which may be verified by examining samples taken out. There are now added 10 ml. of epichlorohydrin, and the reaction is caused to proceed at 50°C. overnight. Gel formation will take place after 2 hours.

In the morning of the following day the reaction is interrupted, whereupon acetone is added to the reaction mixture. After decanting off the solvent from the gel grains, a new portion of acetone is added and decanted off to remove substantially the whole amount of cellulose-acetate-butyrate. In order to remove the film of the polymer stabilizing agent surrounding the grains, the latter are dispersed in a solution of 50:50 aqueous 2N solution of sodium hydroxide and 95 per cent ethyl alcohol. After treating the gel grains for 15 minutes therewith, there is added a diluted solution of hydrochloric acid to neutralize the grains, whereupon the mixture is filtered. The gel grains are shrunk by treating them with ethyl alcohol and finally dried at 70°C. in vacuum.

The copolymer contains 10% of acetone. The yield of copolymer, calculated on material free from acetone, is 90 g. The water regain is 19.2 g./g. of the dry product and the swelling factor 38 ml./g. of the dry product.

Distribution of size: 6.2% 100—200 mesh  
51.5% 200—270 mesh  
40.2% 270—400 mesh  
2.1% <400 mesh

## EXAMPLE 7

100 g. of dextrin, produced by hydrolysing starch under acid conditions, are dissolved in a solution of 200 ml. of water and 125 ml. of aqueous 5N solution of sodium hydroxide, and the solution formed is dispersed in a solution of 15 g. of cellulose-acetate-

butyrate in 500 ml. of ethylene dichloride at 50°C. 40 ml. of epichlorohydrin as a cross-linking agent are added to the dispersion, and the cross-linking reaction is caused to proceed at 50°C. for 18 hours. After purification and drying as set forth in Example 6, there will be obtained 100 g. of a product having a water regain amounting to 4.8 g./g. of the dry product.

Size distribution: 24% 100—200 mesh  
66% 200—400 mesh  
10% <400 mesh

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## EXAMPLE 8

120 g. of dextran having an average molecular weight amounting to 20,000 are moistened with 30 ml. of water and to the mixture obtained are added 95 ml. of an aqueous 5N solution of sodium hydroxide to form an aqueous solution of the dextran. The solution is dispersed in a solution of 10 g. of cellulose-acetate-butyrate in 250 ml. of ethylenedichloride. The dispersion is heated to 50°C., and to it are added at this temperature 80 g. of ethylene glycol-diglycidyl ether, whereupon the mixture is allowed to react for 18 hours.

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After working up and drying as set forth in Example 6, there will be obtained 157 g. of a copolymer having a water regain amounting to 2.1 g./g. of the dry product.

Distribution of size: 15 g. 30—50 mesh  
102 g. 50—100 mesh  
31 g. 100—200 mesh  
6 g. <200 mesh

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EXAMPLE 9  
120 g. of 2-hydroxypropyl dextran ( $M_w=5.10^4$ ) are dissolved in 200 ml. of water, and to the solution are added 60 ml. of aqueous 5N solution of sodium hydroxide. The solution formed is dispersed in a solution of 10 g. of cellulose-acetate-butyrate in 250 ml. of ethylene dichloride at a temperature of 50°C. 10 ml. of epichlorohydrin are added, and the reaction is caused to proceed at this temperature for 18 hours.

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After working up the reaction mixture and drying the reaction product as set forth in Example 6, there will be obtained 102 g. of a copolymer of 2-hydroxypropyl dextran with epichlorohydrin having a water regain amounting to 7.3 g./g. of the dry product.

Distribution of size: 5 g. 50—100 mesh  
60 g. 100—200 mesh  
36 g. <200 mesh

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EXAMPLE 10  
60 g. of ethyl hydroxyethyl cellulose are dissolved in 350 ml. of water, and to the solution are added 30 ml. of an aqueous 5N solution of sodium hydroxide. The solution

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formed is dispersed in a solution of 10 g. of cellulose-acetate-butyrate in 250 ml. of ethylene dichloride, whereupon 10 ml. of epichlorohydrin are added as a cross-linking agent.

5 The suspension is heated to 50°C. and maintained at this temperature for 18 hours, whereupon the reaction mixture is worked up and the gel grains dried. There are obtained 43 g. of a copolymer of hydroxyethyl cellulose with epichlorohydrin having a water regain amounting to 7.1 g./g. of the dry product.

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Distribution of size: 8 g. 100-200 mesh  
27 g. 200-400 mesh  
15 5 g. <400 mesh

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## EXAMPLE 11

50 g. of spray-dried dextran ( $M_w=40,000$ ) are dissolved in 50 ml. of water, and to the solution obtained are added 4 ml. of an aqueous 2N solution of sodium hydroxide. The solution of dextran is then dispersed in a solution of 3 g. of cellulose-acetate-butyrate in 100 ml. of ethylene dichloride. To the dispersion are then added 10 ml of 1.2-3.4-25 diepoxybutane as a cross-linking agent and the mixture is heated to 50°C., whereupon the reaction is permitted to proceed overnight. The reaction mixture is worked up and the gel grains are dried as set forth in Example 1. There are obtained 50 g. of a copolymer of dextran with 1.2-3.4-25 diepoxybutane having a water regain amounting to 5.0 g./g. of the dry product.

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## EXAMPLE 12

35 100 g. of starch washed with water are dissolved in 230 ml. of water and 240 ml. of an aqueous 5N solution of sodium hydroxide. The solution obtained is dispersed in a solution of 15 g. of cellulose-acetate-butyrate in 40 500 ml. of ethylene dichloride. After stirring the dispersion for an hour, in order to stabilize the drops of starch solution in the dispersing medium, are added 70 g. of 1,3-dichloropropane-2-ol. The reaction is caused 45 to proceed for 16 hours at 50°C. After working up the reaction mixture as set forth in Example 6, there is obtained 93 g. of a copolymer in gel grain form presenting a water regain of 3.3 g./g. of the dry product.

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## EXAMPLE 13

50 20 g. of polyvinyl alcohol are dissolved in 140 ml. of water and 60 ml. of an aqueous 5N solution of sodium hydroxide. The solution obtained is dispersed in a solution of 8 g. cellulose-acetate-butyrate in 200 ml. of ethylene dichloride. To the dispersion obtained are added 20 ml. of epichlorohydrin and the reaction is caused to proceed for 16 hours at 50°C. and for 4 hours at 70°C. 55 After working up the reaction mixture according to what is set forth in Example 6, there

is obtained a copolymer presenting a water regain of 9.1 g./g. of the dry product.

Distribution of size: 60% 20-50 mesh  
30% 50-100 mesh  
10% >100 mesh

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## EXAMPLE 14

120 g. of dextran ( $M_w=40,000$ ) are moistened with 36 ml. of water, whereupon the moistened dextran is dissolved in 144 ml. of an aqueous 3N solution of sodium hydroxide. The solution of dextran is dispersed in a solution consisting of 300 ml. of ethylene dichloride and 30 g. of a 27 per cent solution of polymethylmethacrylate in ethyl acetate. After a stabilizing period of 30 minutes there are added 30 ml. of epichlorohydrin, and the reaction is caused to proceed for 16 hours at 50°C. The gel grains obtained are separated off by filtration, rinsed first with ethylene dichloride and then with 99.5 per cent ethyl alcohol, after which they are dispersed three times in water, decantation being carried out between the dispersing operations. The gel grains are finally shrunk with 99.5 per cent alcohol. After drying at 60°C. the product weighs 120 g. and presents a water regain of 6.2 g./g. of the dry product.

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## EXAMPLE 15

120 g. of dextran ( $M_w=20,000$ ) are moistened with 30 ml. of water, and the moistened dextran is dissolved in 120 ml. of an aqueous 5N solution of sodium hydroxide. The dextran solution is dispersed in a solution of 6 g. of polyvinyl butyral ( $M_w=70,000$ ) in 300 ml. of ethylene dichloride, 40 ml. of epichlorohydrin are added, and the resulting reaction is caused to proceed at 50°C. for 16 hours. The gel grains are filtered off and dispersed 4 times in 500 ml. acetone each time between the dispersion operations. Any remaining polyvinyl butyral is rinsed away by dispersing the grains in aqueous 1N hydrochloric acid for 10 minutes. Finally, the copolymer is washed with water, shrunk with 99.5 per cent alcohol and dried. The product obtained weighs 110 g. and presents a water regain of 2.5 g./g. of the dry product.

## WHAT WE CLAIM IS:—

1. In a method for the manufacture of high molecular weight hydrophilic copolymer as hereinbefore defined of hydroxyl group-containing non-ionic polymer substances in the form of gel grains, in which a hydroxyl group-containing non-ionic polymer substance is reacted, in the presence of an alkaline reacting substance, with a bifunctional organic substance capable of reacting with the hydroxyl groups of the uncharged polymer substance with formation of ether bridges

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in the molecular proportion of 1 mole of the hydroxyl group-containing substance to at least 10 moles of the bifunctional substance, as a cross-linking agent, the improvement which comprises mixing a liquid solution of the non-ionic polymer substance with a dispersing medium capable of forming a two-phase system therewith, under sufficient agitation conditions to transform this liquid solution into drops suspended within the medium, and reacting the cross-linking agent with the non-ionic polymer substance in the presence of said alkaline reacting substance until gel formation has taken place, and recovering the gel grains of the copolymerisate, formed from the drops. 45

2. A method as claimed in claim 1, in which the alkaline reacting substance is contained in the solution of the non-ionic polymer substance. 50

3. A method as claimed in claim 1, in which the alkaline reacting substance is contained in the dispersing medium. 55

4. A method as claimed in claim 1, in which the alkaline reacting substance is added to the two-phase system. 60

5. A method as claimed in any of claims 1 to 4 in which the cross-linking agent is contacted with the solution of the non-ionic polymer substance on the formation of the two-phase system. 65

6. A method as claimed in any of claims 1 to 4, in which the whole amount of the cross-linking agent is contacted with the non-ionic polymer substance without permitting gel formation to take place before forming the two-phase system. 70

7. A method as claimed in any of claims 1 to 4, in which a portion of the cross-linking agent is contacted with the non-ionic

polymer substance before forming the two-phase system without gel formation being permitted to take place and the remaining portion of the cross-linking agent is supplied to the two-phase system. 75

8. A method as claimed in any of claims 1 to 5 or 7, in which at least a portion of the cross-linking agent is supplied dissolved in the dispersing medium.

9. A method as claimed in any of claims 1, 2, 6 or 7, in which a solution of the non-ionic polymer substance, the alkaline reacting substance and the cross-linking agent is maintained at a sufficiently low temperature to prevent gel formation and the two-phase system is then formed.

10. A method as claimed in any of claims 1 to 9, in which the degree of dispersion is controlled by adding a high molecular weight water-insoluble polymer immiscible with the solvent having the non-ionic polymer substance dissolved therein.

11. A method as claimed in any of claims 1 to 10, in which the amount of the high molecular weight water-insoluble polymer is in the range of from 0.1 to 15, inclusive, grams per 100 ml of the dispersing medium.

12. A method as claimed in any of claims 1 to 11, in which the high molecular weight substance is capable of undergoing hydrolysis under mild conditions.

13. A method as claimed in claim 1 and substantially as hereinbefore described with reference to the Examples.

14. The product of the method of any one of claims 1 to 13.

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